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(54) Title: COMPOSITIONS CONTAINING MICROPARTICLE MATRICES

(57) Abstract

A sustained release drug-polymer microparticle matrix comprising an active drug having basic properties and a blend of pharmaceutically acceptable polymers or copolymers.

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COMPOSITIONS CONTAINING MICROPARTICLE MATRICES

This invention relates to drug-containing polymer matrix systems, in particular to such systems offering controlled, sustained and preferably pH-independent drug release, their preparation, pharmaceutical compositions containing them, and their use in therapy.

Microencapsulation is a coating technology well known for use with orally administrable drug materials. The incorporation of drug materials into a drug-polymer matrix by the general process known as solvent evaporation is also known. Matrices formed by solvent evaporation processes have the active substance dispersed throughout the matrix structure. They are thus distinguished from drug microcapsules which have a distinct polymer outer wall.

Matrix structures formed by a solvent evaporation process which gives rise to discrete drug-polymer particles may be either homogeneous, microporous systems or heterogeneous, macroporous systems. Matrix particles are termed homogeneous when the drug is distributed uniformly throughout the polymer structure such that the particles have a transluscent appearance. Macroporous matrix particles have a two-phase heterogeneous construction consisting of a dispersion of separate drug and polymer phases. The different refractive indices of the two phases result in turbidity of the polymer matrix and confer an opaque appearance on the matrix particles.

Both microencapsulation of drug materials and matrix formation offer a number of advantages over standard drug delivery systems. These include:

(a) modification of the physical properties of drugs, for example by providing liquid drugs in solid form, and the preparation of free-flowing powders;

(b) the taste masking of bitter drugs and means for concealing unpleasant odours;

(c) the provision of means for the controlled and sustained release of drugs.

GB 2 166 651 A (Elan Corporation) relates to a controlled release drug powder containing discrete microparticles (termed pharmasomes) for use in sustained release compositions and made by solvent evaporation processes. The microparticles contain an active ingredient, at least one non-toxic polymer and an optional excipient uniformly distributed throughout the microparticle matrix. Pharmasomes prepared from a wide range of drugs and polymer or copolymer materials are disclosed. The working examples describe microparticles prepared from polymer and copolymer materials including inter alia cellulose acetate butyrate, ethyl cellulose and Eudragit RS-100. Eudragit RS-100 is a copolymer of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups with chloride ion counter-ions. (Eudragit is a trade name of Rohm Pharma).

European Patent Application, Publication Number 0 212 641 (Searle) relates to a porous drug-polymer matrix, prepared by a solvent evaporation process, and comprising an active ingredient having basic properties and a pharmaceutically acceptable copolymer having a plurality of carboxylic acid and ester groups (an anionic copolymer) which matrix releases the active ingredient in a medium having a pH value less than 4. The porous drug-polymer matrices of the invention are described as having utility in masking the

taste of the active ingredient and effecting its release in the acid environment of the stomach. Porous matrices as described in EPA-0 212 641 are distinguished from microcapsules prepared by complete coating of an active ingredient with a film of anionic polymer material in that microcapsules give rise to significant release of active ingredient only at alkaline pH, the polymeric film being insoluble at acid pH values. The porous nature of the drug-polymer matrix is described as enhancing the release of active ingredient in acidic media. Taste-masking compositions prepared from anionic polymers and copolymers including Eudragit L-100 and Eudragit S-100 are described. Eudragit L-100 and S-100 are copolymers of methacrylic acid and methyl methacrylate.

Japanese Kokai Publication, JP 63174925 (Hisamitsu Pharmaceutical Co.) relates to pharmaceutical microcapsules prepared by a solvent evaporation process and comprising an active drug material and an acrylic macromolecular copolymer. Microparticles are prepared from a range of copolymer materials with active ingredients having acidic properties and are described as having either sustained release properties or a dissolution profile dependent on pH.

It has now been found that by blending polymer materials having differing chemical properties, drug polymer microparticle matrices can be prepared offering both taste-masking and a sustained and controlled drug release profile of practical benefit.

It has also been found that drug release from drug-polymer microparticle matrices is dependent not only on the properties of the polymer material and the drug but also on the physical properties of the matrix, which are in turn dependent on the solvent evaporation conditions under which the matrix is prepared. For example, a homogeneous microparticle matrix prepared from drug materials having

basic properties and anionic polymer materials, such as Eudragit L-100 or S-100, has been found to release drug under both acid and alkaline conditions, the release being more rapid at alkaline pH than at acid pH. It has also been shown that release of drug from homogeneous microparticles prepared from drug materials having basic properties and neutral polymeric materials such as Eudragit RS-100, is dependent on the pH of the dissolution medium, in this instance the release rate being more rapid at acid pH values.

Furthermore, it has surprisingly now been found that a drug-polymer matrix can be prepared conferring both taste-masking and sustained release properties but wherein the drug release profile is independent of the pH of the dissolution medium. Drug-polymer matrices of this type have particular utility in sustained release compositions for oral administration.

Accordingly, the present invention provides a sustained release drug-polymer microparticle matrix comprising an active drug having basic properties, a pharmaceutically acceptable anionic polymer or copolymer, and a pharmaceutically acceptable neutral polymer or copolymer. In a preferred aspect, the invention provides a drug-polymer matrix, as defined, which is homogeneous. More preferably, the invention provides a drug-polymer matrix, as defined, which is homogeneous and confers a drug release profile that is substantially independent of the pH of the dissolution medium.

Drug release which is independent of the pH of the dissolution medium is particularly advantageous for orally administrable compositions. It will be appreciated that when administered by this route, the <u>in vivo</u> rate of drug release will be independent of the pH variation encountered on passage through the gastro-intestinal tract. This ranges from alkalinity in the mouth conferred by the saliva,

through the acid environment of the stomach, to the alkaline conditions of the intestine. Furthermore, it has surprisingly been found that drug-polymer microparticle matrices of the invention conferring pH-independent drug release have enhanced sustained-release properties.

A drug-polymer matrix of the invention has a dissolution profile wherein the rate of drug release is directly proportional to the square root of time. This is characteristic of a matrix containing dispersed or dissolved drug and indicative of a diffusion-controlled mechanism for drug-release.

Drug-polymer matrices of the invention are prepared by a solvent evaporation process which confers a microparticle construction. Preferably the microparticles are homogeneous and have a compact, substantially spherical and non-porous structure which enhances the sustained release properties of the matrix.

The size of the microparticles of the invention is preferably below 150μm, more suitably below 60μm and preferably below 20μm. A small particle size has the advantage in formulations for oral administration, more especially in liquid formulations, of a non-gritty texture conferring an acceptable mouth-feel. Particle size is suitably determined by sieve analysis.

Active drug materials having basic properties for use in drug-polymer matrices of the invention include drugs having basic functional groups, for example amino groups, which are capable of ionic interaction with polymer material. An ionic interaction contributes to the taste masking and sustained release properties of the matrix and is of particular utility in liquid formulations. A wide range of active drug materials may be used. Representative of active

drug materials for incorporation into matrices of the invention are drugs such as dextromethorphan, chlorpheniramine, phenylpropanolamine, and also pseudoephedrine, and pharmaceutically acceptable salts thereof. A preferred active drug is the cough supressant, dextromethorphan.

Pharmaceutically acceptable polymer materials for use in drug-polymer matrices of the invention comprise a neutral component and an anionic component. Either component may itself comprise a polymer or copolymer material. As used herein, the term neutral polymer or copolymer denotes a polymer or copolymer which has no functional groups capable of ionic interaction with a basic drug. A preferred neutral component is the copolymer synthesised from acrylic and methacrylic acid esters which is sold under the trade name Eudragit RS-100. Other suitable neutral components include cellulose derivatives such as ethyl cellulose .

As used herein, the term anionic polymer or copolymer denotes a polymer or copolymer which has acidic properties which render it capable of interaction with a basic drug, for example a polymer or copolymer which has appended thereto acidic functional groups capable of ionic interaction with a basic drug material. Suitable anionic components include acrylic acid and methacrylic acid polymers and copolymers thereof, and copolymers based on combinations of acrylic acid and/or methacrylic acid with acrylic acid esters and/or methacrylic acid esters such as methyl acrylate and methyl methacrylate. Preferred anionic components are copolymers based on combinations of methacrylic acid and methyl methacrylate sold under the trade names Eudragit L and Eudragit S. Other suitable anionic components include cellulose acetate phthalate and cellulose acetate butyrate.

The combination of neutral and anionic polymer components is a key feature for pH-independent drug release microparticle matrices of the invention. The neutral component also contributes to the compactness and mechanical strength of the matrix. As referred to above, the anionic component contributes, through interaction with the basic drug, to the sustained release properties of the matrix and additionally confers stability to liquid formulations.

The ratio of neutral component to anionic component may be varied to suit the desired sustained release properties of the matrix. The chosen ratio will of course be dependent on the acidic properties of the anionic component, for example on the number of acidic functional groups in the polymer or copolymer of the anionic component which are available for ionic interaction. It will be appreciated that a predominance of one component may upset the balance which maintains pH-independent drug release. Suitably, where the drug is dextromethorphan and the pharmaceutically acceptable polymer materials are Eudragit copolymers, the neutral and anionic components are present in a weight ratio of 1:1.

The ratio of active drug to pharmaceutically acceptable polymer materials is similarly dependent on the desired sustained release profile of the active drug ingredient. Drug release is dependent on both the physical and chemical properties of the matrix. The sustained release of drug will be enhanced by optimising the extent of the interaction between the drug and the anionic component of the pharmaceutically acceptable polymer materials. Excess drug which is not bound to the anionic component will be released from the matrix more rapidly than drug material which is subject to binding, in particular ionic binding. Drug release will also be influenced by the level of compactness of the microparticles making up the matrix.

The binding capacity of a polymer or copolymer may be readily ascertained by one of ordinary skill in the art by routine experimentation. For example the equilibrium adsorption isotherm technique may be used to determine drug loading so as to optimise both the drug release profile and taste masking effects.

The invention also provides for the preparation of a drug-polymer microparticle matrix of the invention by a solvent evaporation process.

Matrices of the invention are prepared by a solvent evaporation process which comprises:

(i) forming a solution of the pharmaceutically acceptable polymer materials in a solvent;

(ii) dissolving or dispersing the active drug in the polymer solution to achieve a uniform mixture; and

(iii) removing the solvent from the mixture so formed to provide microparticles having a substantially spherical, matrix construction, by use of an external liquid phase.

A solvent evaporation process of the invention preferably provides a drug-polymer microparticle matrix having a homogeneous construction and more preferably a compact, non-porous construction.

Suitable solvents for solubilising the pharmaceutically acceptable polymer materials include organic solvents such as ketones, alcohols, hydrocarbon solvents, and mixtures of any two or more thereof. Preferred solvents, particularly suitable for use with copolymers sold under the trade name Eudragit, include acetone, ethanol, ethyl acetate,

chloroform, dichloromethane, methanol and isopronanol. Preferably, the active drug is soluble in the polymer solution so formed. Generally, the basic drug is added directly to the polymer solution. Alternatively, it may be convenient to dissolve the drug in an organic solvent prior to mixing with the polymer solution. A uniform mixture of the active drug in the polymer solution may be achieved by thorough mixing.

Removal of the solvent to give microparticles having the desired physical characteristics is achieved by adding the drug/polymer/solvent mixture to an external liquid phase with which it is immiscible or partially immiscible in the presence of a dispersing agent; emulsifying the two-phase mixture thus obtained; evaporating the solvent; and isolating the microparticles, suitably by filtration or centrifugation.

Suitable liquids for the external liquid phase include inter alia aqueous solutions, organic solvents, mineral oils and vegetable oils. The liquid chosen for the external liquid phase will be determined according to the selected drug, the pharmaceutically acceptable polymer material and the organic solvent in which it is dissolved.

Suitable dispersing agents include substances such as stearic acid derivatives, for example magnesium stearate and aluminium stearate. A dispersing agent is utilised in order to optimise the microparticle structure. Its concentration may be varied to influence particle size and to confer a compact, and preferably a substantially non-porous structure.

Efficient emulsification of the external liquid phase with the drug/polymer/solvent phase is suitably obtained using a high shear mixer. It has been found that efficient emulsification is a primary requirement for a microparticle

matrix having an average particle size below 150 μm.

Solvent evaporation may be effected at room temperature for volatile solvents or by heating. It is desirable to maintain efficient mixing throughout the evaporation procedure.

Isolation of the microparticle matrix is suitably followed by repeated washing with a suitable solvent to remove traces of the external liquid phase, followed by drying.

The properties of the microparticles of the drug-polymer matrix formed by the process hereinbefore described are influenced by a number of factors.

For example, factors influencing particle size include the rate of emulsification, the amount of dispersing agent, the viscosity and relative quantities of the drug/polymer/solvent and external liquid phases, the configuration of the mixing vessel and stirrer, and the processing temperature.

Factors influencing the configuration and density of the microparticles include the choice of solvent and its rate of evaporation, the molecular weight and crystallinity of the polymer materials and the concentration of dispersing agent.

The invention also provides a pharmaceutical composition comprising a drug-polymer microparticle matrix as hereinbefore defined and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable carriers may include conventional additives and excipients such as preservatives,

binding agents, fillers, tabletting agents, lubricants, disintegrants, suspending agents, buffering agents, flavouring agents and colouring agents.

A pharmaceutical composition of the invention is preferably formulated for oral administration. Compositions may be in the form of tablets including effervescent and chewable tablets, capsules, lozenges, powders and granules. The matrices of the invention are particularly suitable for use in liquid formulation compositions, more especially in liquid formulation compositions for oral administration.

Oral liquid preparations may be in the form of syrups or elixirs or may be presented as a dry product for reconstitution with water or other suitable liquid vehicle before use.

The amount of drug-polymer matrix in a pharmaceutical composition of the invention will be dependent on the chosen active drug and the dosage level required. The quantity of drug-polymer matrix in a composition may be adjusted to deliver an effective dose of a selected drug to a patient in need of treatment. Pharmaceutical compositions may be in unit dose presentation form.

In a further aspect, the invention provides a drug-polymer microparticle matrix, as hereinbefore defined, for use as an active therapeutic substance.

The invention is illustrated but not limited by the following examples in which drug-polymer microparticle matrices are prepared incorporating the cough suppresant dextromethorphan.

The following Examples 1 and 2 and accompanying Figure 1 relate to drug-polymer microparticle matrices of the invention conferring pH-independent drug release. The following Examples 3 and 4 and accompanying Figures 2 and 3 relate to drug-polymer microparticle matrices conferring pH-dependent drug release falling outside the scope of the invention and which are included for comparative purposes.

Drug dissolution was measured according to the basket method of US Pharmacopoiea at 37°C and 100rpm.

Example 1

Preparation of drug-polymer matrix microparticles containing dextromethorphan, Eudragit S-100 and Eudragit RS-100

Disperse Phase:

Eudragit S-100: 3.75g
Eudragit RS-100: 3.75g
Propan-2-ol/Acetone: 100ml (50/50 v/v)
Dextromethorphan hydrobromide: 2.5g

Continuous Phase:

Heavy mineral oil: 400ml
Magnesium stearate: 12g

Polymer materials were added to the mixed solvent in a stoppered conical flask and dissolved over a magnetic stirrer for 60 minutes. Drug was added to the polymer solution and dissolved over a magnetic stirrer for 45 minutes. This constituted the disperse phase.
Mineral oil was added to a 800ml narrow beaker.
Magnesium stearate was added to mineral oil and dissolved over a magnetic stirrer for 60 minutes. This formed the

continuous phase. The disperse phase was added to the continuous phase. The mixture was emulsified with a high shear mixer for 15 seconds. The emulsion was transferred to a 700ml reaction vessel equipped with a glass anchor stirrer, in a water bath. Solvent evaporation was effected by gradual heating, first up to 35°C for 3 hours followed by 60°C for 3 hours. Microparticles were separated from the continuous phase by centrifugation and then washed several times with n-hexane to remove mineral oil completely. Finally, the matrix microparticles were dried at 45°C for 6 hours. Analysis of the matrix microparticles indicated a drug-loading of 16.2% by weight.

Microparticles were graded into different size ranges by sieving (using British Standard test sieves) and examined by scanning electron microscopy. Both test sieving and SEM indicated a particle size range of 0-150μm with 0-50μm being the major size fraction.

The accompanying Figure 1 is a graphical representation of drug release from dextromethorphan/Eudragit S-100/RS-100 matrix particles made according to the above-described procedure. The graph illustrates that drug release is independent of the pH of the dissolution medium and that a substantially uniform release of drug is sustained over a 12 hour period.

Example 2

Preparation of a liquid formulation composition containing dextromethorphan/Eudragit S-100/RS-100 matrix microparticles

A liquid formulation was prepared by suspending microparticles obtained from example 1 in a liquid vehicle (247mg/10ml of vehicle). The vehicle composition was as follows:

Excipient	% by weight
Sorbitol solution	57.2
1,2-Propylene glycol	2.5
Sodium citrate	0.2
Citric acid	0.2
Keltrol	0.7
Sorbic acid	0.1
Sodium benzoate	0.1
Distilled water	39

A particle size fraction of 0-50µm was used.

The weight of microparticles required for the manufacture of the suspension was such as to yield a 40mg/10ml dosage of the drug when in suspension.

Panel tests revealed the microparticle suspension to possess good mouth-feel and to be free from the characteristic bitter taste of dextromethorphan hydrobromide. The formulation was assessed at 18 weeks post-manufacture and found to retain its taste-masking and sustained drug release potential.

Example 3

Preparation of dextromethorphan/Eudragit S-100 matrix microparticles

The general procedure of Example 1 was repeated using Eudragit S-100 as the only polymer material.
The composition of the disperse and the continuous phases was as follows.

Disperse Phase:

Eudragit S-100: 7.5g
Propan-2-ol/Acetone: 100ml (50/50 v/v)
Dextromethorphan hydrobromide: 2.5g

Continuous Phase:

Heavy mineral oil: 400ml
Magnesium stearate: 12g

Scanning electron microscopy and test sieving revealed a particle size range of 0-150µm with 0-50µm being the major size fraction.

The accompanying Figure 2 is a graphical representation of drug release from microparticles of Example 3. The graph illustrates that release of drug from anionic copolymer microparticles is dependent on the pH of the dissolution medium and that drug release is more rapid and more complete at alkaline pH.

Example 4

Preparation of dextromethorphan/Eudragit RS-100 matrix microparticles

The general procedure of Example 1 was repeated using Eudragit RS-100 as the only polymer material. The composition of the disperse and the continuous phases was as follows.

Disperse Phase:

Eudragit RS-100: 30g
Methanol: 70ml
Dextromethorphan hydrobromide: 4.5g

Continuous Phase:

Heavy mineral oil: 300ml
Magnesium stearate: 4.0g

Scanning electron microscopy and test sieving revealed a particle size range of 0-400µm with 180-355µm being the major fraction.

The accompanying Figure 3 is a graphical representation of drug release from microparticles of Example 4. The graph illustrates that release of drug from the neutral copolymer microparticles is dependent on the pH of the dissolution medium and that drug release is more rapid and more complete at acid pH.

Claims

1. A sustained release drug-polymer microparticle matrix comprising an active drug having basic properties, a pharmaceutically acceptable anionic polymer or copolymer, and a pharmaceutically acceptable neutral polymer or copolymer.

2. A sustained release drug-polymer microparticle matrix as claimed in claim 1 wherein the microparticles have a homogeneous construction.

3. A sustained release drug-polymer microparticle matrix as claimed in claim 1 or 2 wherein the microparticles have a compact, substantially spherical and non-porous construction.

4. A sustained release drug-polymer microparticle matrix as claimed in claim 1, 2 or 3 wherein the size of the microparticles is below 150 μm.

5. A sustained release drug-polymer microparticle matrix as claimed in claim 4 wherein the size of the microparticles is below 60 μm.

6. A sustained release drug-polymer microparticle matrix as claimed in any one of claims 1 to 5 wherein drug release is substantially independent of the pH of the dissolution medium.

7. A sustained release drug-polymer microparticle matrix as claimed in any one of claims 1 to 6 wherein the active drug is dextromethorphan, chlorpheniramine, phenylpropanolamine or pseudoephedrine, or pharmaceutically acceptable salts thereof.

8. A sustained release drug-polymer microparticle matrix as claimed in any one of claims 1 to 7 wherein the neutral polymer or copolymer comprises ethyl cellulose or esters of acrylic and methacrylic acids.

9. A sustained release drug-polymer microparticle matrix as claimed in claim 8 wherein the neutral polymer or copolymer is a copolymer of acrylic and methacrylic acid esters.

10. A sustained release drug-polymer microparticle matrix as claimed in any one of claims 1 to 9 wherein the anionic polymer or copolymer comprises acrylic and methacrylic acid polymers or copolymers thereof, copolymers of acrylic and/or methacrylic acid with esters of acrylic and/or methacrylic acids, cellulose acetate phthalate or cellulose acetate butyrate.

11. A sustained release drug-polymer microparticle matrix as claimed in claim 10 wherein the anionic polymer or copolymer is a copolymer of methacrylic acid and methyl methacrylate.

12. A sustained release drug-polymer microparticle matrix comprising dextromethorphan or a pharmaceutically acceptable salt thereof, a copolymer of acrylic and methacrylic acid esters, and a copolymer of methacrylic acid and methyl methacrylate.

13. A sustained release drug-polymer microparticle matrix substantially as hereinbefore described with reference to Example 1.

14. A solvent evaporation process for preparing a sustained release drug-polymer microparticle matrix as defined in any one of claims 1 to 13 comprising.

(i) forming a solution of the pharmaceutically acceptable polymer materials in a solvent;

(ii) dissolving or dispersing the active drug in the polymer solution to achieve a uniform mixture; and

(iii) removing the solvent from the mixture so formed to provide microparticles having a substantially spherical, matrix construction, by use of an external liquid phase.

15. A process as claimed in claim 14 wherein the external liquid phase includes a dispersing agent.

16. A process as claimed in claim 14 or 15 wherein the solvent for the pharmaceutically acceptable polymer materials comprises an organic ketone, alcohol or hydrocarbon solvent, or mixtures thereof.

17. A process as claimed in claim 16 wherein the solvent comprises acetone, ethanol, ethyl acetate, chloroform, dichloromethane, methanol or isopropanol, or mixtures thereof.

18. A process as claimed in any one of claims 14 to 17 wherein the external liquid phase comprises an organic solvent, or a mineral or vegetable oil.

19. A process as claimed in any one of claims 15 to 18 wherein the dispersing agent is a stearic acid derivative.

20. A process for preparing a sustained release drug-polymer microparticle matrix as defined in any one of claims 1 to 13 substantially as hereinbefore described with reference to Example 1.

21. A pharmaceutical composition comprising a drug-polymer microparticle matrix as defined in any one of Claims 1 to 13 and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition substantially as hereinbefore described with reference to Example 2.

23. A pharmaceutical composition for oral administration as a liquid, comprising a suspension of a drug-polymer microparticle matrix as defined in any one of claims 1 to 13 in a pharmaceutically acceptable liquid carrier.

24. A process for preparing a pharmaceutical composition as defined in claim 21, 22 or 23 comprising admixing a drug-polymer microparticle matrix as defined in any one of claims 1 to 13 with a pharmaceutically acceptable carrier.

25. A process for preparing a pharmaceutical composition substantially as hereinbefore described with reference to Example 2.

26. A drug-polymer microparticle matrix as defined in any one of claims 1 to 13 for use as an active therapeutic substance.

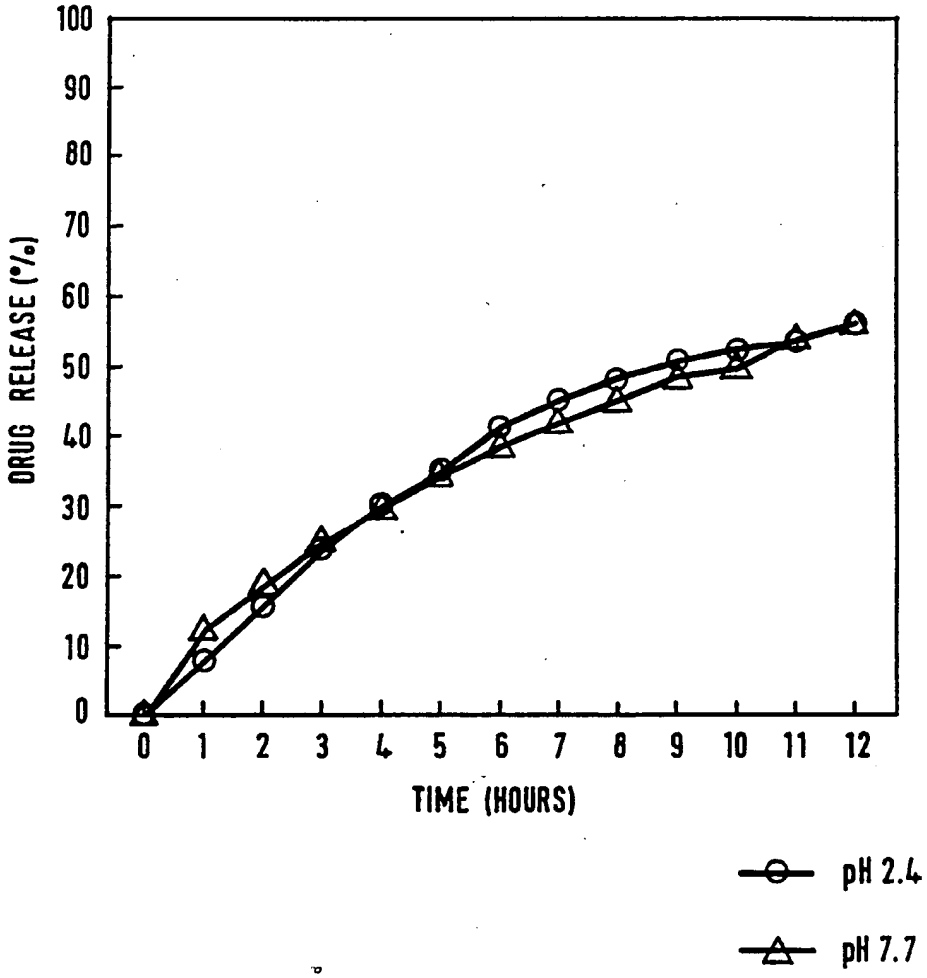
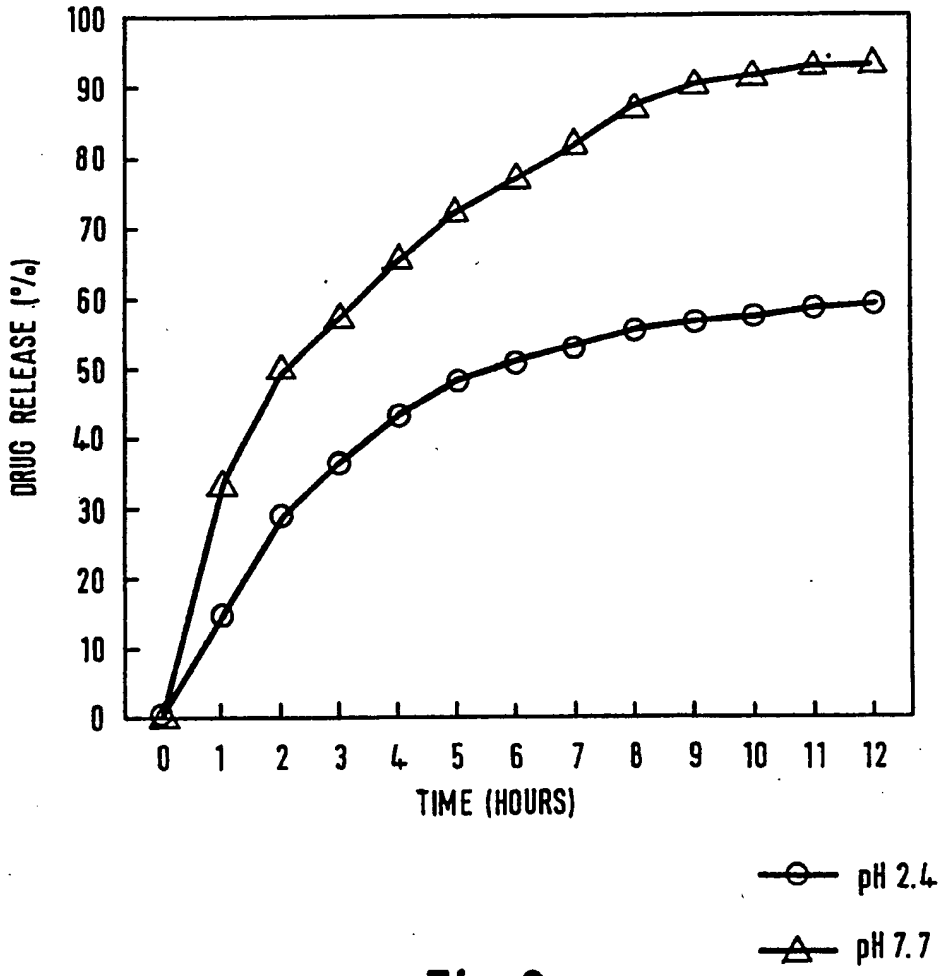

100
90
80
70
60
50
40
30
20
10
0
DRUG RELEASE (%)
0 1 2 3 4 5 6 7 8 9 10 11 12
TIME (HOURS)
pH 2.4
pH 7.7

Fig.1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70
60
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40
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20
10
0
DRUG RELEASE (%)
0 1 2 3 4 5 6 7 8 9 10 11 12
TIME (HOURS)
pH 2.4
pH 7.7

Fig.2

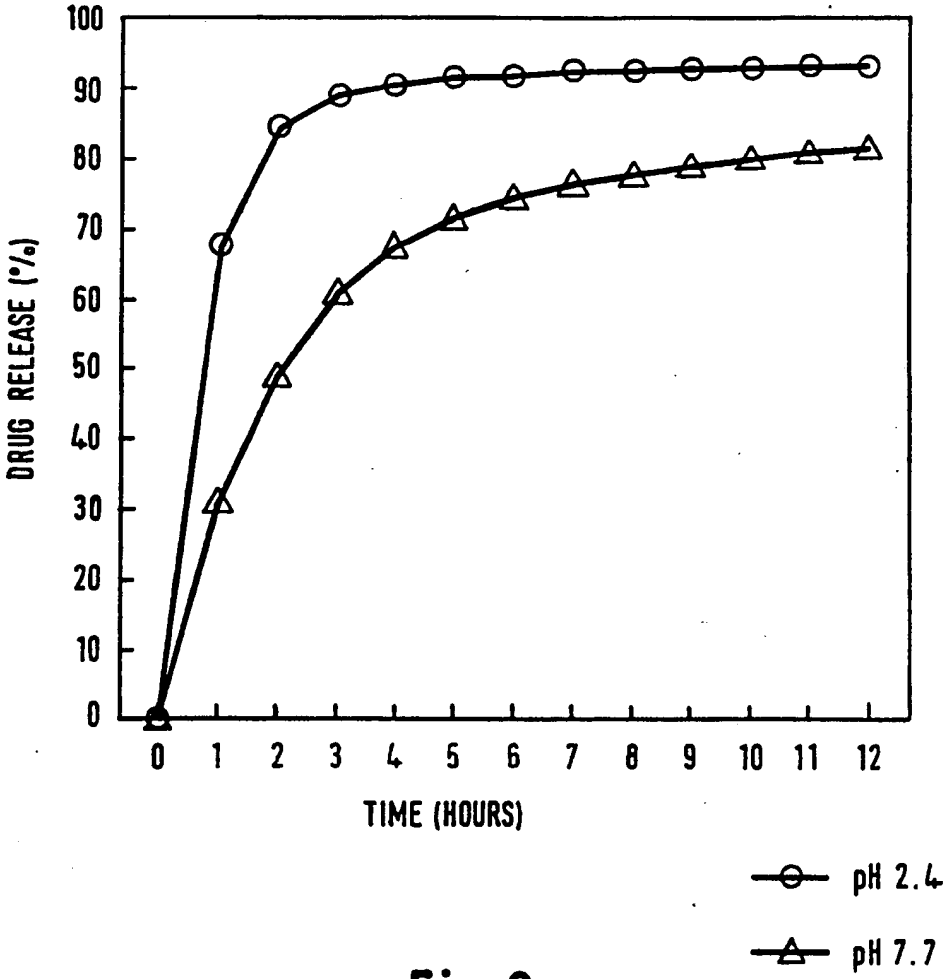
100
90
80
70
60
50
40
30
20
10
0
DRUG RELEASE (%)
0 1 2 3 4 5 6 7 8 9 10 11 12
TIME (HOURS)
pH 2.4
pH 7.7

Fig.3

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01140

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	GB,A,2166651 (ELAN CORPORATION PLC) 14 May 1986, see page 1, lines 22-28, 43-65; page 2, line 60 - page 3, line 9; page 9, example 10; pages 12,13; examples 13,14; claims 1,2,5,15 (cited in the application) ---	1-26
Y	Chemical Abstracts, volume 102, no. 22, 3 June 1985, (Columbus, Ohio, US) Y. Pongpaibul et al.: "Preparation and evaluation of controlled release indomethacin microspheres", see pages 385-386, abstract 191008r, & Drug Dev. Ind. Pharm. 1984, 10(10), 1597-1616 ---	1-26
A	EP,A,0349453 (SOCIETE CORTIAL S.A.) 3 January 1990, see page 2, column 1, lines 3-7; page 2, column 2, lines 19-34; page 3, columns 3-4; example 1; claim 1 --- -/-	1

° Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23-10-1991	04. 12. 91
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Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0014514 (ORION-YHTYMÄ OY) 20 August 1980, see page 1, lines 2-6; page 4, line 18 - page 5, line 4; page 6, lines 4-10; page 13, lines 20-23 ---	1
A	EP,A,0040590 (AB HÄSSLE) 25 November 1981, see page 3, lines 11-20; page 3, line 33 - page 4, line 2; page 7, examples 1,2; claims -----	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101140 SA 49449

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 20/11/91
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